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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,478	12/13/2001	C. Frank Bennett	RTS-0303	6796

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/020,478	BENNETT ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-13-01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 2-5-04.

Claims 1, 2 and 4-26 are pending in the instant application.

Election/Restrictions

Applicant's election with traverse of SEQ ID NO: 3 in Paper No. 2-5-04 is acknowledged. The traversal is on the ground(s) that the restriction should require an election of species, not of an invention. This is not found persuasive because the various nucleotides claimed (e.g. in canceled claim 3) constitute patentably distinct inventions, not species. Each sequence represents a distinct chemical and biological entity and the restriction requirement of the various inventions, not species is correct.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3 and 27 have been canceled and so are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 2-5-04.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims depend from claim 1, which has a 3'-UTR limitation as the target region of SEQ ID NO: 3. These dependent claims, however, are not further limiting from claim 1 because claims 21-25 are drawn to other additional regions of SEQ ID NO: 3, and claim 26 is redundant, because it is drawn to the same region as claimed in claim 1. Appropriate clarification is requested.

Claims 15-20 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of expression of SEQ ID NO: 3, does not reasonably provide enablement for the in vivo targeting and inhibition of SEQ ID NO; 3, nor for treatment in an organism comprising the administration of antisense targeting SEQ ID NO: 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of inhibiting the expression of B-cell associated protein encoded by SEQ ID NO: 3 in vitro and in vivo and treating any disease or condition in an organism comprising the administration of antisense oligonucleotides that target and inhibit the expression of SEQ ID NO: 3.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the

antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting the expression of B-cell associated protein encoded by SEQ ID NO: 3 in an animal. Applicants have not provided guidance for the treatment of diseases or conditions associated with B-cell associated protein comprising the administration of antisense oligonucleotides.

The specification teaches the inhibition of expression of SEQ ID NO: 3 in vitro comprising the administration of antisense oligoncucleotides The specification fails to teach the inhibition of expression of SEQ ID NO: 3 in target cells in an organism comprising the administration of antisense that target SEQ ID NO: 3. And the

specification fails to teach the treatment of any disease or condition associated with the expression of B-cell associated protein in an organism comprising the administration of antisense oligonucleotides. One skilled in the art would not accept on its face the examples given in the specification of the in vitro inhibition of SEQ ID NO: 3 expression as being correlative or representative of the successful in vivo targeting and inhibition of SEQ ID NO: 3, or of the treatment of any disease or condition associated with the expression of B-cell associated protein in an organism comprising the administration of antisense in view of the lack of guidance in the specification and known unpredictability associated with determining the ability of antisense to target and inhibit the target gene in an organism and further whereby treatment effects are provided for any disease or condition associated with the expression of SEQ ID NO: 3. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed, which treatment methods are for any disease or condition associated with the expression of B-cell associated protein in an organism.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods of inhibiting the expression of B-cell associated protein encoded by SEQ ID NO: 3 in vitro and in vivo and treating any disease or condition in an organism comprising the administration of antisense oligonucleotides that target and inhibit the expression of SEQ ID NO: 3. The quantity of experimentation required to practice the invention as claimed would

require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring bacteria in an organism whereby SEQ ID NO: 3 expression is inhibited in vivo, and further whereby treatment effects are provided for any conditions or diseases associated with the expression of B-cell associated protein in an organism comprising the administration of antisense oligonucleotides. Since the specification fails to provide any particular guidance for the targeting and inhibition of expression of SEQ ID NO: 3 in any organism or treatment effects provided in an organism comprising the administration of antisense targeting SEQ ID NO: 3, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-16 and 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Montano et al in view of Milner et al and McKay.

The claims are drawn to compositions methods comprising the administration of antisense oligonucleotides 8-50 nucleobases in length that specifically target various regions of SEQ ID NO: 3 (5'-UTR, coding region, 3'-UTR) and inhibit the expression of SEQ ID NO: 3 in vitro, and which antisense comprise phosphorothioate internucleotide linkages, 2'-O-methoxyethyl sugar moieties, 5-methylcytosine, or which antisense is optionally chimeric, and which compositions further comprise a pharmaceutically acceptable diluent and a colloidal dispersion system.

Montano et al (PNAS 96: 6947-6952, 1999) teach the polynucleotide sequence of SEQ ID NO: 3, encoding human REA (see figure 1 on page 6949) and its role in determining the sensitivity of estrogen target cells, including breast cancer cells, to antiestrogens and estrogens (see abstract on page 6947 and text on pages 6951-2), as well as its role in various cellular processes, including developmental, tumor suppression and senescent processes. (figure 2 on page 6949, text on page 6951).

Montano et al do not teach antisense and methods that specifically target and inhibit the expression of REA of SEQ ID NO: 3 in vitro, nor the incorporation of phosphorothioate internucleotide linkages, 2'-O-methoxyethyl sugar moieties or 5-methylcytosine into antisense oligonucleotides, nor chimeric oligonucleotides, nor

compositions comprising a pharmaceutically acceptable diluent and a colloidal dispersion system.

Milner et al (Nature Biotech. 15: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro (See especially figures 5-7 on pages 539-540).

McKay et al (USPN 6,133,246, 10-17-00) teach compositions comprising antisense oligonucleotides between 8 and 50 nucleobases in length which optionally comprise modified internucleotide linkages including phosphorothioate linkages, modified nucleobases including 5-methylcytosine, modified sugar moieties including 2'-O-methoxyethyl sugars, and wherein the antisense is optionally a chimeric oligonucleotide, and which compositions further comprise a colloidal dispersion system and a pharmaceutically acceptable carrier. McKay et al also teach the in vitro inhibition of various antisense oligonucleotides between 8-50 nucleobases that specifically hybridize with the target gene (see especially col. 6, line 29 through col. 15, line 10; col. 20, line 18 through col. 24, line 67; see also Tables 2 and 3 in col. 37-38).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit the expression of the target gene of SEQ ID NO: 3, encoding B-cell associated protein (a.k.a. REA), because Montano et al disclose the nucleotide sequence of the target REA of SEQ ID NO: 3. It would have been obvious to one of ordinary skill in the art to inhibit the expression of a nucleic acid of known nucleotide sequence encoding REA in vitro using antisense oligonucleotides because

the methods for inhibiting of a target gene of known sequence using antisense had been taught previously by Milner et al. Milner et al additionally teach methods of designing and evaluating antisense which target different regions of a target gene of previously disclosed sequence for their ability to inhibit a target gene in vitro. In addition, McKay et al teach the routine screening of specific antisense oligonucleotides for their ability to inhibit the expression of their corresponding target gene in vitro. One of ordinary skill in the art would have been motivated to inhibit the expression of SEQ ID NO: 3 encoding REA using antisense oligonucleotides because it had been taught previously by Montano that REA plays a role in determining the sensitivity of estrogen target cells (breast cells) to antiestrogens and estrogens, and REA plays a role in important processes including senescence, development and tumor suppression. Furthermore, Montano et al teach the nucleotide sequence of human REA 9SEQ ID NO: 3) and one of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, and also taught McKay to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides for the in vitro inhibition of expression REA. One of ordinary skill in the art would have been motivated to incorporate the nucleobase, internucleotide linkage and sugar modifications, as well as chimeric structures, into antisense oligonucleotides because such modifications (including 5-methyl cytosine, 2'-O-methoxyethyl and phosphorothioate linkages) have been taught previously by McKay et al to increase target binding, cellular uptake and antisense stability. One of ordinary

skill in the art would have been motivated to utilize pharmaceutically acceptable diluents in order to achieve the appropriate concentration of antisense oligonucleotides for administration to target cells in a manner which is compatible for maintaining cellular integrity and antisense stability and one would have been motivated to utilize colloidal dispersions in order to enhance antisense stability and cellular delivery of antisense, as taught by McKay et al. One of ordinary skill in the art would have expected that the delivery of modified antisense to target cells harboring REA, which antisense specifically hybridize with the target nucleic acid encoding REA (i.e. of SEQ ID NO: 3), would lead to inhibition of expression of REA in vitro.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ
4-30-04